Asp9-Asn (exon 2) and Asn291-Ser (exon 6), in decreased LPL activity and reduced HDL-C levels amongst patients with familial combined hyperlipidaemia. We investigated the potential influence of these mutations upon serum lipids/ lipoproteins amongst the representative, homogeneous, adult male population of Caerphilly.
Methods: 2,316 men were purposely recruited into the Caerphilly Prospective Heart Disease Study, when they were aged between 45-59 years, to prospectively screen and monitor them for CHD and its risk factors. DNA was available for genotyping on 1,958 men from the phase 2 collection. We genotyped them for these mutations and the data was assessed using non-parametric statistical analyses.
Results: The T2 (Asp9-Asn) and R2 (Asn291-Ser) alleles denote restriction sites for the TaqI and RsaI enzymes, respectively. Men possessing the T1 allele had significantly raised levels of apo-A1 (131.3 mg/dl vs 124.9 mg/dl, p=0.009), the major surface protein activating HDL. Whilst individuals possessing the R2 allele had significantly reduced HDL-C levels (0.90 mmol/l vs 1.02 mmol/l, p=0.006) and increased TC/ HDL-C ratios (6.73 vs 5.84, p=0.043). Interestingly, our cohort did not have any R2R2 homozygotes.
Conclusions: Our data suggests that the LPL gene influences lipids/ lipoproteins and dyslipidaemia amongst the UK adult, male population.

1083-70 **Modulation by TGF-Beta1 of Oxidized-LDL-Induced Upregulation of P-Selectin and ICAM-1 and Monocyte Adhesion in Human Coronary Endothelial Cells**

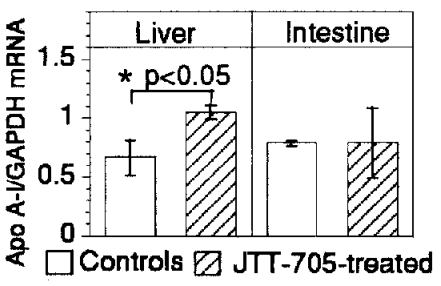
Jawahar L. Mehta, Hongjiang Chen, Dayuan Li, *University of Arkansas for Medical Sciences, Little Rock, Arkansas, Central Arkansas Veterans Healthcare System, Little Rock, Arkansas.*

Background: Oxidized-LDL (ox-LDL) upregulates expression of LOX-1, a specialized lectin-like receptor, on endothelial cells. Upregulation of LOX-1 is associated with expression of adhesion molecules and monocyte adhesion to endothelial cells. This mechanism may relate to the pathogenicity of ox-LDL in atherogenesis. Further, TGF-beta1 has been postulated to exert tissue protective and anti-atherogenic effect. We designed this study to investigate the role of TGF-beta1 in ox-LDL-induced expression of adhesion molecules and monocyte adhesion to human coronary artery endothelial cells (HCAECs).
Methods and results: Fifth generation cultured HCAECs were incubated with native-LDL or ox-LDL (10-40 mg/ml) for 1-24 hrs. Parallel sets of HCAECs were treated with a specific antibody to LOX-1 (10 mg/ml) or to recombinant TGF-beta1 (2 ng/ml) before incubation with ox-LDL (40 mg/ml). Incubation of HCAECs with ox-LDL, but not native-LDL, significantly increased expression P-selectin and ICAM-1 (Western analysis) and monocyte adhesion to HCAECs (all $P<0.01$ vs. n-LDL, n=5). Ox-LDL also decreased active TGF-beta1 levels (measured by ELISA) in a time- and concentration-dependent manner ($P<0.05$ vs. control). Antibody to LOX-1 attenuated the reduction in TGF-beta1 levels ($P<0.05$ vs. ox-LDL alone). Simultaneously, recombinant TGF-beta1 reduced the expression of P-selectin and ICAM-1, as well as monocyte adhesion to HCAECs induced by ox-LDL (all $P<0.02$, n=5).
Conclusion: This study shows that 1) ox-LDL decreases active TGF-beta1 levels by activation of LOX-1; 2) the reduction in active TGF-beta1 may be the basis of ox-LDL-mediated upregulation of P-selectin and ICAM-1 expression and monocyte adhesion to HCAECs.

1083-71 **A Cholesteryl Ester Transfer Protein Inhibitor Increased In Vivo Synthetic Rates and Liver mRNA Levels of Apolipoprotein A-I**

Eiso Shimoji, Bo Zhang, Ping Fan, Keijiro Saku, *Fukuoka University, Fukuoka, Japan.*

Background: Patients with cholesteryl ester transfer protein (CETP) deficiency have increased HDL-C levels, and the inhibition of CETP activity has been shown to increase apolipoprotein (apo) A-I levels and suppress the progression of atherosclerosis in cholesterol-fed rabbits. To clarify the mechanism by which CETP inhibition increases serum apo A-I levels, the effects of a CETP inhibitor, JTT-705, on in vivo apo A-I kinetics and tissue apo A-I gene expression were investigated.
Methods: Japanese White rabbits were randomly fed a diet with (n=8, treated) or without (n=10, controls) 0.75% JTT-705 (Japan Tabacco Inc.) for 7 mo. CETP activities and serum levels of apo A-I and HDL-C levels were measured. Apo A-I kinetics were performed by injecting radioiodinated apo A-I, which was freshly prepared by the guanidine HCl method. Apo A-I mRNA levels in the liver and intestine were quantified by SYBR real-time RT-PCR.
Results: JTT-705 inhibited 32.0% of the CETP activity and increased ($p<0.05$) the serum levels of HDL-C and apo A-I (66.5 ± 13.7 vs. 42.9 ± 6.2 mg/dL). Treated rabbits had a greater ($p<0.05$) synthetic rate (SR) of HDL-apo A-I than control rabbits (13.1 ± 2.6 vs. 10.0 ± 1.9 mg/Kg/day), while the fractional catabolic rates in the two groups were similar (0.47 ± 0.10 /day and 0.52 ± 0.09 /day). JTT-705 increased apo A-I mRNA levels in the liver but not in intestine (Figure).
Conclusion: Increased SR and liver gene expression of apo A-I contribute to the increased serum apo A-I levels induced by CETP inhibition.



1083-95 **Mutation in the Promoter Region of the Hepatic Lipase Gene Correlates With Dyslipidemia in Type 2 Diabetes**

Raj K. Mattu, Edward W. Needham, Jasper Trevelyan, Dimitri J. Richter, Maria A. Adiseshiah, Mauro Lencioni, Shane Gieowarsingh, D. John Betteridge, *University Hospitals Coventry & Warwickshire & University of Warwick, Coventry, United Kingdom, University College London Medical School, London, United Kingdom.*

Background: Cardiovascular disease remains the major cause of morbidity and mortality amongst type II diabetics. The total coronary heart disease risk of these patients is much higher than for non-diabetics at every level of given risk factor, such as dyslipidaemia. About 40% of diabetics have hypertriglyceridaemia (HTG) and reduced high-density lipoprotein cholesterol (HDL-C). Hepatic lipase (HL) is a key enzyme in the hydrolysis of triglycerides in the core of remnant lipoprotein particles and facilitates activation of HDL particles. It therefore influences serum triglyceride and HDL-C levels and may be an important determinant of the dyslipidaemia observed amongst diabetics. A C-514-T mutation involving the promoter region of the HL gene associates with reduced HL activity and increased HDL2 levels, hence we examined whether this mutation related to serum lipids amongst type II diabetics.
Methods: We recruited 386 consecutive patients attending the diabetes clinic. All cardiovascular risk factors were characterised and studied once the patient's diabetic control had become satisfactory. Patient lipids were analysed without lipid modifying drugs. Patients were genotyped using the polymerase chain reaction.
Results: Triglyceride levels were significantly higher (3.25 vs 2.53 mmol/l, p=0.03) amongst diabetics possessing the TT genotype. Furthermore, subjects possessing the C-514-T promoter mutation had a 78% increased risk of being in the highest tertile of the total cholesterol/ HDL-C ratio distribution, O.R. 1.78 (1.00-3.17, p=0.048).
Conclusions: Mutation of the promoter region of the hepatic lipase gene may predispose type II diabetic patients to a deleterious lipid profile and possibly influence their coronary heart disease risk.

1083-96 **Increasing Testosterone Lowers High Density Lipoprotein Cholesterol by Decreasing Apolipoproteins AI and AII**

John A. Morrison, Dennis L. Sprecher, Bruce A. Barton, *Children's Hospital Medical Center, Cincinnati, Ohio, Maryland Research Institute, Baltimore, Maryland.*

Background: During puberty, high density lipoprotein cholesterol (HDL-C) and its major associated apolipoproteins (apo), AI and AII, decrease markedly in males, but not in females, resulting in the recognized sex differences in lipid profiles and attendant risk to coronary heart disease. The timing of the changes has implicated sex steroid hormones, especially free testosterone (T) in the changes. Previous studies of pubertal males have been limited by small samples, cross sectional designs, or longitudinal designs using only two points in time, design elements that restrict the power of the studies.
Methods: To explicate the role of free T in the pubertal changes in adolescent male lipids we followed 251 black and 283 white males, ages 10-15 yrs at enrollment, for three years. We measured lipid profiles, free testosterone (T), estradiol, and body mass index (BMI = kg/m2) every 6 months and apo AI and AII annually.
Results: Controlling for pubertal stage, black males had higher HDL-C, apoAI, (all $p<.001$), and apoAII ($p=.06$) than white males. With advancing pubertal stage, HDL-C, apoAI and AII decreased in both black and white boys. Longitudinal, multivariate analyses (General Estimating Equations) showed that increasing free T associated with decreasing HDL-C, apo AI and AII (all $p<.01$), but did not affect the ratio of HDL-C to apoAI and AII. When apoAI and AII were entered into the model for changes in HDL-C as predictors, they contributed significantly to decreases in HDL-C. At this point, however, free T dropped out of the model, suggesting that the effects of free T on HDL-C are mediated through apoAI and AII concentrations. Increasing BMI associated with lower HDL-C and HDL-C/(apoAI and AII) ratios but did not associate with changes in apoAI. Estradiol was not associated with changes in HDL-C, apo AI or AII.
Conclusions: During puberty, increasing T appears to contribute to lower HDL-C by lowering the apolipoproteins (apoAI and AII) available to these particles, not by altering the amount of lipid associated with these protein moieties.

POSTER SESSION

1084 Optimal Lipid Control: New Approaches

Monday, March 18, 2002, 9:00 a.m.-11:00 a.m.
Georgia World Congress Center, Hall G
Presentation Hour: 9:00 a.m.-10:00 a.m.

1084-90 **Ezetimibe Co-Administered With Simvastatin in 668 Patients With Primary Hypercholesterolemia**

Michael Davidson, Thomas McGarry, Robert Bettis, Lorenzo Melani, Leslie Lipka, Alexandre LeBeaut, Ramachandran Suresh, Steven Sun, Enrico Veltri, for the Ezetimibe Study Group, *Chicago Center for Cardiovascular Research, Chicago, Illinois, Oklahoma Foundation for Clinical Research, Oklahoma City, Oklahoma.*

Background: This Phase III, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of ezetimibe (EZE) administered with simvastatin (SIM) in pts with primary hypercholesterolemia.
Methods: After dietary stabilization (NCEP Step I or stricter diet), a 2-12 wk screening/ washout period and a 4-wk, single-blind, PBO lead-in period, 668 pts with baseline LDL-C ≥145 mg/dl to ≤250 mg/dl and TG ≤350 mg/dl were randomized to 1 of the following administered daily for 12 consecutive wks: EZE 10 mg; SIM 10, 20, 40 or 80 mg; EZE mg